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Coincident Acute Myelogenous Leukemia and Ischemic Heart Disease: Use of the Cardioprotectant Dexrazoxane During Induction Chemotherapy

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Treatment of acute myelogenous leukemia is challenging in the setting of ischemic heart disease because anthracycline and anthracenedione drugs used in induction chemotherapy may potentiate myocardial dysfunction. We have managed two patients with coincident acute myelogenous leukemia and ischemic heart disease with the cardioprotectant drug dexrazoxane (ICRF-187), administered before each dose of mitoxantrone or idarubicin. Both patients tolerated their induction chemotherapy, developed marrow hypoplasia from chemotherapy, and achieved clinical remission. Dexrazoxane may have a role as a cardioprotectant in the treatment of select patients with acute myelogenous leukemia. Am. J. Hematol. 59:246–248, 1998. © 1998 Wiley-Liss, Inc.

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INTRODUCTION

Standard induction chemotherapy for acute myelogenous leukemia is a combination of an anthracycline or an anthracenedione drug and the antimetabolite, cytosine arabinoside [1]. Anthracycline or anthracenedione-induced cardiotoxicity [2–5] becomes a major clinical concern in the setting of pre-existing heart disease [6]. Dexrazoxane (ICRF-187) is a recently available iron chelating agent that has been shown to reduce anthracycline cardiotoxicity in patients receiving chemotherapy for breast cancer and sarcoma [7–12]. We have managed two patients with coincident acute myelogenous leukemia and ischemic heart disease with dexrazoxane in an attempt to limit cardiotoxicity in this setting.

Patient No. 1

A 70-year-old white man with a history of two myocardial infarctions and coronary artery revascularization was admitted to the coronary care unit of St. Mary's Hospital with right shoulder pain and dyspnea relieved with nitroglycerin. Electrocardiogram confirmed the presence of prior anterior and inferior wall myocardial infarctions, and revealed an incomplete left bundle branch block and frequent premature ventricular contractions. No evidence of acute myocardial infarction was found on admission by serial electrocardiograms or serum enzymes. However, a two-dimensional echocardiogram confirmed an ischemic cardiomyopathy with left atrial and left ventricular dilatation. The left ventricular ejection fraction was estimated at 30% by both echocardiography and radionuclide angiocardiography.

Admission white blood cell count was markedly elevated at 107,000/mm^3 with a predominance of immature monocytoid cells. A bone marrow aspirate confirmed the presence of acute myelomonocytic leukemia of cell surface antigen phenotype CD33+, CD15+, CD14+, and CD11c+. The patient was managed initially with oral hydroxyurea and leukapheresis with a decrease in the white blood cell count to 18,000/mm^3 48 hr after admission. Induction chemotherapy consisted of mitoxantrone, 10 mg/m^2 (18 mg) intravenous bolus daily for

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three days plus cytosine arabinoside, 25 mg/m^2 (45 mg) intravenous bolus, followed by 100 mg/m^2 (180 mg) per day continuous infusion for a planned seven-day course.

Given the baseline low cardiac ejection fraction and suggestion by history of active ischemic heart disease, it was thought advisable for the best interest of the patient to administer a cardioprotectant drug before the mitoxantrone. Therefore, dexrazoxane 500 mg/m^2 (900 mg) was administered as a slow intravenous bolus daily 30 min before mitoxantrone. In addition, the patient was continued on his pharmaceutical regimen for left ventricular dysfunction including captopril, furosemide, digoxin, and topical nitroglycerin. Cardiopulmonary function remained stable throughout treatment as assessed by clinical parameters by three observers. The white blood cell count dropped to 800/mm^3 by day 5 of chemotherapy and bone marrow aspirate and biopsy on day 9 were markedly hypocellular with no residual leukemia.

Because of development of cellulitis, cytosine arabinoside was discontinued after five days of treatment and granulocyte-monocyte colony-stimulating factor 250 μg/m^2 per day was initiated in an attempt to limit the time of neutropenia. White blood cell count increased to 3,800/mm^3 by day 21 and a bone marrow sample from day 36 showed normal cellularity with no residual leukemia.

The patient experienced sudden death at his home a few weeks later thought to be due to cardiac arrhythmia.

Patient No. 2

A 43-year-old man with a history of cocaine ingestion was admitted to the coronary care unit of St. Mary's Hospital with chest pain, anemia, and thrombocytopenia. Electrocardiogram revealed T wave inversions in the inferior and anterolateral leads, and serum creatine kinase total concentration and MB fraction were elevated consistent with a non Q wave acute myocardial infarction. The patient was stabilized with nitroglycerin, β-blockers and aspirin, and no arrythmia or clinical heart failure occurred. Echocardiogram revealed a normal left ventricular ejection fraction of 70%.

Admission white blood cell count was 5,400/mm^3, hematocrit was 23%, and platelet count was 33,000/mm^3. Myeloblasts with Auer rods were visible in peripheral blood and bone marrow samples, and the diagnosis of acute myelogenous leukemia was confirmed by cell surface antigen phenotype (CD34+, CD13+) and chromosomal translocation 8;21. The patient was treated with idarubicin, 12 mg/m^2 (28 mg) intravenous bolus daily for three days and cytosine arabinoside, 25 mg/m^2 (57 mg) intravenous bolus followed by 200 mg/m^2 (460 mg) intravenous infusion daily for seven days. Concern for the risk of idarubicin-induced cardiac toxicity was great because of the concurrent acute myocardial infarction. Therefore, dexrazoxane, 1,000 mg was administered intravenously over 15 min before each dose of idarubicin. No acute cardiac toxicity developed and the patient did well clinically for two weeks with an aplastic bone marrow sample obtained on day 14.

On day 17, while severely neutropenic, the patient developed a fever of 39.5°C with rigors, tachypnea, hypoxia, hypotension, and bilateral alveolar infiltrates on chest radiograph. The patient improved over six days with oxygen, antibiotics, careful fluid management, and pharmacologic management with an angiotensin converting enzyme inhibitor, digoxin, and furosemide. His white blood cell count improved by day 26 and he was discharged. A bone marrow sample on day 49 showed normal cellularity and chromosome analysis was normal. An echocardiogram on day 66 showed a left ventricular ejection fraction of 60%. At that point, the angiotensin converting enzyme inhibitor and digoxin were discontinued and a β-blocker was started, which he tolerated very well.

The patient subsequently received two cycles of high-dose cytosine arabinoside chemotherapy for consolidation and he remains in clinical remission.

DISCUSSION

Dexrazoxane is a bispiperazinedione derivative of ethylenediaminetetraacetic acid (EDTA) and is a potent intracellular chelating agent. The compound is available commercially as Zinecard® (Pharmacia and Upjohn, Kalamazoo, MI) and has been shown to reduce doxorubicin-induced cardiotoxicity in patients treated for breast cancer and sarcoma [7–12]. The mechanism of action of dexrazoxane is not fully understood, although in laboratory models it interferes with iron-mediated free radical generation thought to be responsible, in part, for anthracycline-induced cardiomyopathy.

Although the risk of anthracycline-induced cardiomyopathy is greatest in patients who have received high cumulative doses of these agents, cardiac damage can occur in patients receiving standard regimens as used to treat acute myelogeneous leukemia [3,6]. The risk of clinical congestive heart failure is higher in patients with pre-existing heart disease [6].

Reports of dexrazoxane as a cardioprotectant in the treatment of acute myelogenous leukemia are limited, although results are encouraging in two small series of patients in relapse treated with daunorubicin and mitoxantrone [13,14]. In addition, dexrazoxane has been shown to be synergisitic with anthracyclines against L1210 leukemia in mice [15]. We treated two patients with acute myelogenous leukemia with dexrazoxane as a component of initial induction therapy due to coincident evidence of ischemic heart disease. Both patients were treated following informed written consent. Both tolerated induction therapy well, developed marrow hypopla-

sia from chemotherapy as expected in conventional circumstances, and achieved clinical remission.

Patient no. 1 had frequent premature ventricular complexes on electrocardiogram before receiving chemotherapy, and his sudden death approximately two months after treatment from presumed arrythmia is thought to be related to the patient's underlying heart disease rather than a late effect of mitoxantrone or dexrazoxane. The cardio-pulmonary decompensation on day 17 for patient no. 2 was thought to be related to infection because of the presence of fever, rigor, and neutropenia and clinical recovery correlating with improvement in his neutrophil count.

The recommended dose of dexrazoxane is a 10:1 ratio to the concurrent dose of doxorubicin. However, idarubicin and mitoxantrone are more potent and more toxic drugs on a mg-per-mg basis and are customarily administered at approximately one-fifth the dose of doxorubicin [16–19]. Dexrazoxane was found to be cardioprotective in mice receiving idarabicin at dose ratios greater than or equal to 10:1 [20]. A dose ratio of dexrazoxane to mitoxantrone of approximately 50:1 was used successfully for two reported patients treated for relapsed acute myelogenous leukemia [14]. Therefore, we chose to administer dexrazoxane at approximately 50 times the dose levels of idarubicin and mitoxantrone used in these patients, resulting in dexrazoxane doses that were similar to those used in clinical studies with doxorubicin. No adverse reactions to dexrazoxane were observed in these two patients.

The clinical use of chemoprotectant drugs is expanding [21]. Dexrazoxane may have a role as a cardioprotectant in the treatment of selected patients with acute myelogenous leukemia.

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